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Diagnostic performance of percutaneous lung biopsy using automated biopsy needles under CT-fluoroscopic guidance for ground-glass opacity lesions

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Objective: The goal of our study was to evaluate the diagnostic performance of percutaneous lung biopsy under CT-fluoroscopic guidance for ground-glass opacity (GGO) lesions.

Methods: 85 percutaneous needle lung biopsies were performed in 73 patients. Specimens were obtained by core biopsy utilising an automated cutting needle and were evaluated histologically. Final diagnosis was confirmed by independent surgical pathology, independent culture results or clinical follow-up.

Results: Rates of adequate specimens obtained and of precise diagnosis by needle

biopsy were 92.9% (79/85) and 90.6% (77/85) of evaluated lung lesions, respectively. Precise diagnosis was achieved in 87.1% (27/31) of lesions ≤ 10 mm in diameter, 90.0% (36/40) of lesions >10 mm to ≤ 20 mm and 100.0% (14/14) of lesions >20 mm. Precision in diagnosing GGO lesions according to the GGO component was 73.9% (17/23) for pure GGO lesions and 96.8% (60/62) for part-solid GGO lesions. Obtaining a precise diagnosis did not differ significantly according to the lesion size ($p=0.3840$), but differences were significant according to the GGO component ($p=0.0047$). Malignancy was accurately diagnosed in 35 of 36 malignant lesions for which surgery was later performed. The

specific cell type determined from specimens obtained by needle biopsy was exactly the same as the final histological diagnosis obtained after surgery in 20 lesions.

Conclusion: Tissue-core lung biopsy under CT-fluoroscopic guidance for a GGO lesion

provides a high degree of diagnostic accuracy but is less reliable for determining the specific cell type.

Advances in knowledge: Percutaneous lung biopsy under CT-fluoroscopic guidance for GGO is useful in differentiating malignancy.

With recent advancements in diagnostic imaging with high-resolution CT, an increase in the detection of ground-glass opacity (GGO) lesions has been noted [1–3]. GGO is a finding on high-resolution CT that is defined as hazy increased attenuation of the lung with preservation of bronchial and vascular margins [4]. GGO can be caused by the combined effects of diminished intra-alveolar air and increased cellular density, with alveolar cuboidal cell hyperplasia, thickening of the alveolar septa and partial filling of the terminal air spaces [5]. GGO is a non-specific finding that may be associated with various disorders including inflammatory diseases, focal fibrosis, atypical adenomatous hyperplasia (AAH), bronchioloalveolar carcinoma (BAC) and adenocarcinoma [5–7].

Lung cancers with a wide area of GGO have been reported to have a good prognosis, and, in most cases, their pathological features are minimally invasive [8–12]. Thus, these tumours are considered to be candidates for limited surgical resection such as segmentectomy and wedge resection although some would consider lobectomy as the most appropriate [13–15]. Additionally, treatment options for BAC, based on the perspective that it is an early phase cancer that has not metastasised, would not be limited to surgical resection but could also include less invasive strategies such as radio-frequency ablation, cryoablation therapy, stereotactic radiotherapy and heavy charged particle radiotherapy [15]. Other lesions might also be considered for less invasive treatments.

Thus, a process to confirm the diagnosis of GGO histologically before starting treatment is required [15]. Although CT-guided lung biopsy, which is well accepted as being effective with high diagnostic accuracy [16–18], would be useful for diagnosing GGO lesions, reports of its use for this purpose have been few [15, 19–21]. In the present study, we evaluated the diagnostic performance of percutaneous lung

biopsy under CT-fluoroscopic guidance for GGO lesions.

Here, we must note that the term BAC is being abandoned after the recent publication of a new lung adenocarcinoma classification under the joint sponsorship of the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [22]. Because most of the subjects of this retrospective and observational clinical study are those with data collected before the new classification became generally used in our institution, we use the term BAC in this report.

MATERIALS AND METHODS

Subjects

Among percutaneous lung biopsies performed under CT-fluoroscopic guidance in our institution between April 2008 and March 2012, 85 lung biopsies were for GGO lesions in 73 patients (38 females and 35 males, mean age 68.5 years and age range 41–88 years). These are the subjects of this study. Two chest radiologists identified GGO lesions on CT by consensus. Images were displayed with a lung window setting (centre, –600 HU; width, 1500 HU). Two biopsies were performed for the same lesion in nine patients on different days, and four biopsies were performed in one patient on different days. The mean diameter of the lesions was 14.0 ± 6.8 mm [$\pm$ standard deviation (SD)] with a range of 4–30 mm (≤ 10 mm, $n=31$; >10 mm to ≤ 20 mm, $n=40$; >20 mm, $n=14$). Their mean depth as measured from the pleural surface to the edge of the mass was 21.0 ± 16.9 mm (range 0–70 mm). In 46 lesions, the percentage of the GGO component was $>90\%$ and was 50–90% in 39. The mean duration of clinical follow-up of a GGO lesion before percutaneous lung biopsy was 11.3 ± 14.3 months (range 1–77 months and median 5 months). An 18-gauge Monopty™ biopsy needle (Bard, Covington, GA), which is a fully automated

Figure 1. A 76-year-old male with a ground-glass opacity (GGO) lesion undergoing tissue-core biopsy of the lung under CT-fluoroscopic guidance. (a) Helical CT image with the patient in the prone position obtained just before the biopsy procedure shows the GGO lesion with no solid part (diameter: 12.7 mm) in the left upper lobe (arrow). (b) Real-time CT-fluoroscopic scan shows the tip of an 18-gauge tissue-core biopsy needle penetrate the GGO lesion (arrow). Note that the I-ITM device (Hakko, Tokyo, Japan), which is a device that assists in precisely advancing the needle while avoiding irradiation to the operator's hands, is seen (arrowhead).

(a)

(b)

cutting needle, was used for 71 procedures. For the other 14 procedures, an 18-gauge TemnoTM needle (Bauer Medical, Clearwater, FL), which is a semi-automated cutting needle, was used. It is also our standard practice to use 18-gauge cutting needles for lung biopsies of solid lesions.

Biopsy procedures

All patients had undergone diagnostic CT of the chest with contiguous axial tomographic sections before the biopsy (Figure 1). At the time of the biopsy, preliminary helical CT images were obtained in 5-mm-thick sections through the lesion. From a review of these preliminary images, patient position, level of the needle entry site and direction of the approach for the biopsy were planned to provide the most direct route for biopsy, to traverse the least amount of aerated lung and to avoid bullae and fissures. During biopsy, patients assumed a supine ($n=30$), prone ($n=40$) or lateral ($n=15$) position. The CT unit used was the X Vigor LaudatorTM (Toshiba Medical System, Tokyo, Japan).

The procedure was performed by one of four interventional radiologists experienced in CT-guided biopsy after obtaining informed consent from the patient. A CT-fluoroscopic imaging system was used for all CT-guided biopsy procedures. Details of CT-fluoroscopy have been described elsewhere [23]. Imaging parameters during CT-fluoroscopy included a CT beam width collimated to 3 mm, a tube voltage of 120 kVp, a current of 30–50 mA and a scanning speed of 0.75 s per rotation (360°). An operator wearing a protective lead apron in the CT room was responsible for the control of CT-fluoroscopic exposure via a foot pedal and assisted in table movement and gantry tilt and directed the laser light beam via the control panel. The control panel was covered with a sterile transparent drape when a single operator performed the procedure. Alternatively, an assistant would help by adjusting the controls. An intermittent real-time CT-fluoroscopic technique [24] was preferred while the biopsy needle was advanced using the I-ITM device (Hakko, Tokyo, Japan) that was developed to assist in precisely advancing the needle while avoiding irradiation to the operator's hands [25, 26]. This technique was performed in a stepwise manner with quick application of CT-fluoroscopy to confirm the path of the needle. Patients who could not co-operate with breath-holding underwent the procedure during usual respiration. After

confirming that the needle tip had reached the lesion, a specimen was obtained and the needle was withdrawn. When the operator was uncertain as to whether the needle tip had reached the lesion or if the specimen was insufficient, rebiopsy was performed.

All biopsy procedures were performed under local anaesthesia. After the biopsy procedure, axial CT images were obtained during a single breath-hold through the level of the biopsy or, if necessary, through the whole chest using helical CT scanning to evaluate the presence of complications such as pneumothorax. While still on the scanner table, patients with a moderate or severe pneumothorax or with symptoms of pneumothorax underwent immediate manual aspiration of air from the pleural space using an 18- or 20-gauge intravenous catheter or chest tube placement, if necessary, according to methods reported by Yankelevitz et al [27] or Yamagami et al [28]. Those patients with pneumothorax were

transferred to the recovery room where oxygen was administered by nasal cannula (100.0% at 3 l min⁻¹).

Specimens obtained by tissue-core biopsy were evaluated histologically. All histological evaluations were performed by experienced chest pathologists who were required not only to classify obtained specimens as positive or negative for malignancy but also to identify specific cell types, if possible.

Investigated parameters

The ability to determine from the biopsy specimens whether the lesion was malignant or benign and to characterise specific cell types was evaluated. The sensitivity, specificity and accuracy of CT-fluoroscopy-guided lung biopsy for diagnosing GGO were calculated. Diagnostic ability was compared according to the lesion size (≤ 10 mm, >10 mm to ≤ 20 mm and >20 mm) and the GGO component. The GGO component on CT images was classified into the following three categories: lesions with no solid component, those with a solid component ≤ 5 mm and those with a solid component >5 mm.

Statistical analysis was performed using the χ^2 test for independence of the ability to differentiate a malignant from a benign lesion according to the lesion size and the GGO component.

The final diagnosis was confirmed by independent surgical pathology ($n=40$), independent culture results ($n=1$) or clinical follow-up ($n=44$). Clinical proof of a malignant lesion was accepted if the patient was treated for malignancy provided that the subsequent clinical course and response to therapy were appropriate. Clinical proof of a benign lesion was accepted if any of the following three conditions were satisfied: (1) spontaneous resolution, (2) resolution after treatment for conditions other than cancer, such as antibiotic treatment, and (3) no change in lesion size on follow-up CT.

RESULTS

The mean time required for biopsy procedures was 19.7 ± 6.4 min (9–53 min). This included the entire period during which the patient was on the CT scanner table, and therefore included time for urgent management of cases with biopsy-induced complications, such as immediate percutaneous manual aspiration for

Table 1. Characterisation of specific cell types obtained by percutaneous lung biopsy

Diagnosed specific cell types	<i>n</i>
Malignancy	58
Adenocarcinoma	17
Adenocarcinoma with BAC	24
BAC	11
Non-small cell carcinoma	2
Metastasis	4
No malignancy	27
Atypical adenomatous hyperplasia	2
Atypical mucus epithelial cell hyperplasia	1
Bronchiolitis	1
Chronic interstitial pneumonia	1
Cryptococcosis	1
Epithelioid granuloma	2
Fibrosis	5
IgG4-related sclerosing disease	1
Organising pneumonia	2
Pneumonitis	5
Inadequate material for diagnosis	1
Lung tissue	5
Total	86

BAC, bronchioloalveolar carcinoma; Ig, immunoglobulin.

Table 2. Results of CT-fluoroscopy-guided lung biopsy of 85 ground-glass opacity (GGO) lesions

Size		True positive	True negative	False positive	False negative
≤10 mm	n=31	16	11	0	4
>10 mm and ≤20 mm	n=40	30	6	0	4
>20 mm	n=14	12	2	0	0
Total	n=85	58	19	0	8
GGO component		True positive	True negative	False positive	False negative
With no solid part	n=23	13	4	0	6
With solid part ≤5 mm	n=23	19	4	0	0
With solid part >5 mm	n=39	26	11	0	2
Total	n=85	58	19	0	8

complicated pneumothorax. The average number of punctures by the biopsy needle was 1.6 ± 0.6 (median 1; range 1–4).

Table 1 shows specific cell types for lesions obtained by percutaneous lung biopsy. In 79 (92.9%) of the 85 procedures, materials appropriate for pathological analysis were obtained. Of the 85 specimens, 77 (90.6%) were accurately diagnosed as either positive or negative for malignancy (true positive, $n=58$; true negative, $n=19$) (Table 2). Overall, the sensitivity, specificity and accuracy of CT-fluoroscopy-guided percutaneous core biopsy for diagnosing GGO lesions were 87.8%, 100.0% and 90.6%, respectively. The sensitivity, specificity and accuracy according to the size were 80.0%, 100.0% and 87.1%, respectively, with lesions ≤10 mm; 88.2%,

100.0% and 90.0%, respectively, with lesions >10 mm to ≤20 mm; and 100.0%, 100.0% and 100.0%, respectively, with lesions >20 mm. There was no significant difference in the ability to achieve a precise diagnosis according to the lesion size ($p=0.3840$, χ^2 test for independence). The sensitivity, specificity and accuracy in diagnosing GGO lesions according to the GGO component were 68.4%, 100.0% and 73.9%, respectively, for GGO lesions with no solid component; 100.0%, 100.0% and 100.0%, respectively, for GGO lesions with a solid component ≤5 mm; and 92.9%, 100.0% and 94.9%, respectively, for GGO lesions with a solid component >5 mm. With regard to differences in obtaining a precise diagnosis according to the GGO component in the lesion, the rate was significantly lower for GGO lesions with no solid component than

Table 3. Characterisation of specific cell type as proved by histological examination in cases for which surgery was performed

Needle biopsy	Surgery			
	Adenocarcinoma	Adenocarcinoma with BAC	BAC	Metastasis
Adenocarcinoma	5	3	0	0
Adenocarcinoma with BAC	4	11 ^a	2	0
BAC	2	3	3	0
Metastasis	0	0	0	1
Atypical adenomatous hyperplasia	0	1 ^a	1	0
Pneumonitis	4 ^b	0	0	0
Total	15	18	6	1

BAC, bronchioloalveolar carcinoma.

^aIncluding a case in which needle biopsy was performed twice.

^bCases for which needle biopsy was performed four times for one lesion.

for those with a solid component ($p=0.0047$ according to the χ^2 test for independence).

Surgery was subsequently performed for 36 malignant lesions for which 40 biopsy procedures had been performed. As shown in Table 3, malignancy was accurately diagnosed in 34 of the 40 procedures (85.0%). The specific cell type determined from the material obtained by needle biopsy corresponded completely to the final histological diagnosis after surgery in 20 of these lesions. In one lesion, needle biopsy was repeated four times in 21 months, with the diagnosis of pneumonitis each time. However, the final histological diagnosis after surgery was adenocarcinoma in this patient. This GGO lesion was 16 mm and had no solid component.

Regarding biopsy-induced complications, pneumothorax, which was the most frequent complication in the present study, appeared on CT images performed immediately after biopsy in 44 (51.8%) of the 85 procedures. Immediate manual aspiration was performed in 7 of these patients, and further treatment with chest tube insertion was necessary in 3 (3.5%) out of 85. In 9 (10.6%) cases, haemoptysis occurred after biopsy. None of the patients had serious complications.

DISCUSSION

Percutaneous image-guided lung biopsy has found widespread acceptance as a principal method of diagnosing lung nodules. Modalities commonly employed include fluoroscopy [29], conventional CT [30] and helical CT [30], with the last becoming more widely used. CT-fluoroscopy, which was developed more recently than the other modalities and used in the present study, has simplified the process and decreased the time required for CT-guided needle biopsies [24]. Regarding direct exposure of the physician's hand to radiation, which is a problem with CT-fluoroscopy-guided procedures, the use of a needle holder, such as the "I-I device" that was used in the present study, can largely resolve this problem. According to Irie et al [25], the radiation dose to the physician's hand using the needle holder was less than one-tenth of that without such a holder.

The success rate in obtaining sufficient samples for cytohistological evaluation (rate of adequate biopsy) has been reported to range from 80% to 100% [30–41].

The most common complication of CT-guided lung biopsy is pneumothorax, with a frequency ranging from 17.9% [30] to 54.3% [34] according to previous reports [30, 31, 41–47]. These reports reveal a frequency of chest tube placement ranging from 2.0% [43] to 15.0% [34] of all biopsy procedures. Haemoptysis is also well known as a biopsy-induced complication, with a frequency ranging from 2.0% [47] to 10.1% [33]. The technical success rate for obtaining adequate specimens and frequency of biopsy-induced complications in the present study was similar to those in previous reports.

In previous reports of CT-guided lung biopsy, sensitivity, specificity and accuracy of this method to diagnose malignancy accurately were reported to be 77–97% [32, 34–36], 71–100% [32–36] and 62–93% [32–37], respectively. Diagnostic accuracy has tended to decrease in parallel with decreases in lesion size [33, 35]. It has been suggested that the use of real-time CT-fluoroscopic guidance can improve diagnostic ability even for smaller lesions [17].

Undoubtedly, the purpose of lung biopsy is to differentiate malignant from benign lesions. Further, it is necessary to determine the specific cell type because treatment of lesions proved to be malignant by needle biopsy is selected based on the cell type. When a lesion is proven to be benign, clarification of the specific cell type may also be necessary. Otherwise, for example, a diagnosis of simply "negative for malignancy" would indicate the necessity for long-term follow-up or biopsy with another procedure [34] because, in some cases, lesions not diagnosed according to the specific cell type are found to be malignant on second biopsy or the follow-up study [29]. Controversy exists about whether cytology or histology is more useful in the diagnosis of lung nodules. However, histological evaluation of specimens obtained by tissue-core biopsy utilising an automated cutting needle is more advantageous than cytology in the ability to make a specific diagnosis. This is especially the case with benign lesions [36], if an on-site cytopathologist is absent or if frozen section analysis cannot be performed at the time of biopsy [32]. In previous reports of CT-guided tissue-core biopsy of lung nodules, the specific cell type could be characterised in 60–99% of malignant lesions and 44–91% of benign lesions that were evaluated histologically [31, 32, 34, 36, 48]. According to a report in which both fine-needle aspiration evaluated cytologically and core

biopsy evaluated histologically were performed for lung lesions [48], the rate of determination of the cell type was significantly higher with core needle biopsy (94.4%) than with fine-needle aspiration (85.6%) in lesions revealed to be malignant by CT-guided lung biopsy. In addition, the rate of determination of the cell type was also significantly higher with core needle biopsy (68.2%) than with fine-needle aspiration biopsy (9.1%) in lesions revealed to be benign.

Currently, with regard to the automated cutting needle used in performing tissue-core biopsy, the fully automated cutting needle is considered to be a more useful device for obtaining specimens of lung nodules for histological evaluation than semi-automated biopsy needles [18]. According to Yamagami et al [17], in their study comparing specific cell types as revealed by tissue-core biopsy using a fully automated cutting needle with those determined by surgical findings, the specific cell type was characterised by percutaneous tissue-core biopsy in 99 (95.2%) of 104 lesions from which an adequate specimen was obtained. 76 (98.7%) of 77 lesions diagnosed as malignant and 23 (85.2%) of 27 diagnosed as benign from samples obtained by tissue-core biopsy were characterised specifically. Cell types that were determined by tissue-core biopsy in 65 (84.4%) malignant and 23 (85.2%) benign lesions were exactly the same as those proven by surgical pathology.

The subjects of the current study were limited to those with GGO lesions in which an automated cutting needle was used for needle biopsy performed under CT-fluoroscopic guidance. In the majority, a fully automated cutting needle was used. The ability to obtain adequate specimens (92.9%) and diagnostic ability to detect malignant lesions as indicated by sensitivity (87.8%), specificity (100.0%) and accuracy (90.6%) were similar to previous studies of percutaneous tissue-core biopsy for solid lung nodules as described above, although the mean number of punctures was very small at 1.6. From this, the usefulness of tissue-core needle biopsy under CT guidance for determining whether a GGO lesion is malignant or benign can be concluded. Precision rates were high even for small lesions. For example, 87.1% of lesions ≤ 1.0 cm were precisely diagnosed. However, accuracy in diagnosing whether a GGO lesion was malignant or benign differed according to the composition of the GGO component. Accuracy was significantly lower in GGO lesions with no solid part.

Indeed, results were also good with regard to the ability to characterise the specific cell type. In 79 (92.9%) of 85 lesions, a determination of cell type was made. However, out of the 36 lesions for which surgery was performed, specific cell types as diagnosed by percutaneous tissue-core biopsy were exactly the same as the cell types subsequently revealed by surgery in only 20 (55.6%) lesions. This is lower than that reported for tissue-core biopsy performed with an automated cutting needle for solid lung nodules [17]. Furthermore, we must note that, in eight cases diagnosed as BAC by needle biopsy, the final diagnosis was adenocarcinoma in two, suggesting that needle biopsy could not always distinguish between adenocarcinoma and BAC. In other words, even when the lesion was diagnosed by needle biopsy as BAC, which is considered to be an early phase cancer that has not metastasised, it is still controversial whether the results of needle biopsy are sufficient to make a decision as to whether to perform limited surgical resection or employ a less invasive treatment alone. In addition, it should be noted that one lesion was diagnosed as pneumonitis by needle biopsy four times during a 21-month period but that the final diagnosis as revealed by surgery was adenocarcinoma. This suggests that long-term follow-up with images such as CT is necessary in some cases.

In 2011, a new lung adenocarcinoma classification was published by the IASLC, ATS and ERS [22]. According to the new classification, AAH continues to be considered to represent a precursor of adenocarcinoma, although this hypothesis has not yet been confirmed. AAH is defined as a small (usually ≤ 5 mm) focal proliferation of mild to moderately atypical type pneumocyte and/or Clara cells lining the alveolar walls. With this new classification, the term BAC is no longer used. On the other hand, new concepts were introduced, such as adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas with either pure lepidic growth (AIS) or predominant lepidic growth with invasion of 5 mm or less (MIA). AIS and MIA are usually non-mucinous, and only rarely are mucinous. Invasive adenocarcinomas are classified by the predominant pattern after using comprehensive histologic subtyping with lepidic (formerly most mixed subtype tumours with non-mucinous BAC), acinar, papillary and solid patterns; “micropapillary predominant” was added as a new histological subtype.

Variants include invasive mucinous adenocarcinoma (formerly mucinous BAC) and colloid, foetal and enteric adenocarcinoma. This classification would influence the next revision of the tumour, node, metastasis (TNM) staging classification. Studies have shown a close correlation between histological and CT findings [11, 49, 50]. On CT, AAH tends to present as a small pure GGO lesion that typically measures <5 mm in diameter but can be as large as 1–2 cm. Non-mucinous AIS tends to present as a pure GGO lesion >5 mm in diameter. It may also manifest as a part-solid GGO lesion caused by the presence of structural collapse. Mucinous AIS, although rare, may present as a solitary solid nodule. CT findings of MIA have not yet been fully described. Non-mucinous MIA may present as a pure GGO or part-solid GGO lesion with a small solid component corresponding to the area of stromal invasion ≤5 mm. Mucinous MIA is less frequent and presents as a solid nodule. MIA has an excellent prognosis with almost 100% disease-specific survival, similar to AIS. Invasive adenocarcinoma usually manifests as a solid nodule or part-solid GGO lesion, only rarely appearing as having pure GGO [49].

In the present retrospective and observational clinical study, the previously recognised pathological terms are used because most of the subjects were pathologically diagnosed before the new classification came into use in our institution. Thus, the cases diagnosed as BAC in the present study would belong to the adenocarcinoma group such as AIS or MIA if the diagnosis had been made according to the new classification. In future, a study of pathological comparisons of specimens obtained from needle biopsy and surgical resection according to the new classification would be required to establish the role of percutaneous lung biopsy under CT guidance in strategic management of GGO lesions.

In conclusion, the diagnostic ability and safety of tissue-core lung biopsy using an automated cutting needle under CT-fluoroscopic guidance for GGO lesions equal those for solid lung lesions. However, relatively less reliable was the ability to determine the specific cell type of a specimen obtained by needle biopsy. Thus, surgical resection might be necessary when precise information on the specific cell type must be obtained in planning therapy for GGO lesions.

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